REMARKS

As an initial matter, Applicants respectfully request consideration of the IDS submitted on January 20, 2004 (citing USP 6,593,291 to Green). The undersigned would be most grateful if the Examiner could return an endorsed copy of the PTO-1449 form. Should the Examiner require a copy of the patent, the document will be furnished promptly.

Applicants will be sending a further IDS under separate cover. Consideration of that IDS is respectfully requested. Although it is not believed that any of the references bear on the patentability of the instant claims, it is believed that consideration of the references will further appreciation of the invention.

Claims 10, 12, 27, 29, 31, 33, 35, 37, 39, 41, 59-61 and 63-72 are canceled and new claims 73-74 added. Claims 59-61 and 63-72 have been canceled solely to comply with the Office's restriction requirement. Applicants reserve the right to file subsequent applications on the subject matter encompassed by the canceled claims.

Support for amendments to claims 1, 7, 11, 13, 17, 19, 28, 30, 32, 34, 36, 38, 40 and 42 can be found throughout the specification including the Drawings and claims as filed originally.

In particular, claims 1 and 17 have been amended with language from claims 10 and 12, except that each of the features frameworks (FRs) is now at least about 90% identical to a specified sequence. Support for the amendments can be found in claims 10 and 12 as well as the disclosure at pg. 26, line 25 to pg. 27, line 3; pg. 27, line 17 to pg. 28, line 3.

New claim 73 has been rewritten from claim 7. New claim 74 has been rewritten from claims 51-54, for instance.

No new matter has been added by virtue of the amendments or new claim.

Objections

The specification was objected to on pg. 2, paragraph 5 of the Action. The objection has been addressed by this submission.

At paragraph 6, pg. 2, the Office alleged that the Declaration was defective. A revised Declaration is attached to this submission. It shows, among other things, a change of address for Dr. Neives. The change has been duly initialed and dated as requested by the Examiner.

At paragraph 7, pg. 3, the Office objected to claim 7. The claim has been amended to point out proper dependency. New claim 73 is the same as claim 7 except that it depends from claim 6.

Claims 10-13 were objected to for lacking sequence identifiers. The objection has been addressed by amendment.

The objection to claim 19 as stated on pg. 3, paragraph 9 has been addressed by amendment.

In view thereof, reconsideration and withdrawal of the objection is requested.

Regarding paragraph 2 of the Action at pg. 2, Applicants acknowledge election of the claims of Group I as formulated by the Office. Should the Office deem the embodiment set forth in paragraph 2 allowable, it is expected that a further search will be conducted to include the full breadth of the pending claims.

35 USC §112, second paragraph

Claims 19-20, 27-42, 46-48 and 51-54 stand rejected on the basis of indefiniteness. While Applicants respectfully disagree with the positions taken, basis for the rejections have been addressed by this submission.

A. The rejection of claim 19 has been addressed by amendment.

B. The rejection of claims 46-48 and 51-52 have been addressed by amendment along lines of the Examiner's request.

C. Claim 46 was rejected as indefinite. The claim has been amended as suggested by the Examiner.

35 USC §112, first paragraph, (enablement)

Claims 1-50, 55-58 and 62 stand rejected as lacking enablement. Applicants acknowledge the Office position that the specification is enabling for particular humanized antibodies *i.e.*, antibodies that bind tissue factor and have features mentioned in claims 51-54, for instance (new claim 74 has been written along these lines). See the Action at pg. 4. While Applicants agree that antibodies featured by claims 51-54 are enabled by the specification, they respectfully disagree that remaining claims are not enabled.

As understood, the rejection is grounded on the following contentions set forth in the Action at pg. 5. According to the Office:

> 1) the claims may encompass less than a required number of CDRs and those CDRs, such as they are, may be arranged in any order and may be fused to any human or nonhuman framework sequence. Rudikoff (1979) is cited to support the allegation that minor changes in antibody heavy and light chain regions may alter antigen-binding function.
> 2) the specification does not teach that a functional humanized antibody can be made by replacing the CDR regions of an acceptor antibody with the CDRs of a donor antibody (cites omitted).

With respect to (1), above, it is noted that claim 1 features a humanized antibody that binds specifically to antigen (human tissue factor). The specification defines "antibody" as whole immunoglobin, for instance, which binds TF. Specification at pg.

18, lines 18-29. A "humanized antibody" as recited in claim 1 is defined as having an intact immunoglobin light and heavy chain. See the specification at pg. 26, lines 19-23. A worker would know that each of the light and heavy chains includes sufficient CDRs to assist specific binding to TF. More specifically, the worker would accept that in nearly all cases, each chain will usually have three CDRs. In view of Applicants' definition of "humanized antibody" and depth of knowledge in this field (See the Background) further claim specificity is not needed to enable the worker to make and use the invention as claimed.

Further specificity regarding CDR number is certainly not required in view of Applicants' amendment to claims 1 and 17 (specifying FR sequences).

Also with respect to (1), the Office relies on Rudikoff to support the enablement rejection. However, that reference is over 20 years old and no longer of any particular importance in this field. To the extent the rejection relies on this old and out-of-date reference, it cannot stand. A worker would recognize that the reference as relied on is no longer that relevant, particularly as relied on and in view of substantial advances in the field since 1979.

Turning to position (2), the specification does not need to teach that a humanized antibody can be made by replacing the CDR regions of an acceptor antibody with the CDRs of a donor antibody (sometimes called CDR "swapping" or "CDR grafting"). That information is not generally needed for a worker to make and use the invention.

As discussed below, the specification provides several ways to make the claimed humanized antibody. Should a particular CDR "swapping" or other approach not work to produce the claimed antibody, the specification provides more than ample guidance about other methods that could be used to enable one to make and use the claimed invention.

For instance, in a preferred approach discussed by Applicants in detail, the claimed antibody is made by what is referred to as a "best fit" approach. That strategy does not necessarily rely on CDR "swapping" to achieve results. See pg. 35, line 9 to pg. 36, line 25 (describing the "best fit" approach). According to a preferred embodiment of the "best fit" method, individual framework (FR) regions are mutagenized to resemble corresponding human FR regions. Typically, there is no need to swap CDRs, thus avoiding certain pitfalls mentioned by the Examiner. The technique is explained in detail in Example 9 (describing humanization of a preferred anti-TF antibody (cH36) using the "best fit" method).

At pg. 5 of the Action, claims 4-5 were rejected on grounds that "binding specificity" is not defined by the specification. While Applicants must disagree that a worker would not understand what the phrase means in view of the disclosure, the phrase has been deleted in favor of a more specific thermodynamic constant (K_d).

Also at pg. 5 of the Action, the Office alleged that claims 1-9 and 17:

> recite that the 'humanized' antibodies involved grafting a murine CDR onto the framework and constant domain of a human antibody

Applicants have reviewed claims 1-9 and 17 and cannot find such language. Thus to the extent the rejection relies on it as being part of these rejected claims, it cannot stand. Reconsideration is requested.

As mentioned, the specification provides for a variety of ways to make the claimed antibodies. For instance, certain humanization methods are referred to at pg. 26, lines 19-23; pg. 17, lines 1-17, for instance. In the event anyone of those disclosed methods does not work, the specification provides a more preferred humanization using the "best fit" approach outlined above. See pgs. 35, line 9 to pg. 36, line 25; and Example 9. Accordingly, the specification provides for a number of strategies for making the claimed invention. None would require undue experimentation in view of

Applicants' disclosure and level of skill in the field. Such strategies are certainly not limited to the CDR "swapping" mentioned by the Office although one of skill may wish to choose that method to make certain embodiments of the invention.

Claims 10, 12, 27, 29, 31, 33, 35, 37, 39, 41, 45 and 46 stand rejected for reciting at least 95% amino acid sequence identity to the FR sequences. According to the Office at pg. 6 of the Action:

> There does not appear to be sufficient guidance in the specification as filed as to [know] how the skilled artisan would make and use the various amino acids recited in the instant claims. A person of skill would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences. The specification does not enable one of skill in the art at the time the invention was made to predict the structure of a specific antibody and identify the few key amino acids in the framework necessary to retain the shape, and thus the binding specificity, of the CDRs.

Applicants must respectfully disagree. The specification fully satisfies the "how to make" and "how to use" requirements of §112, especially with respect to the rejected claims.

There is almost universal acknowledgement in the field that an important function of the antibody frameworks (FRs)is to position CDRs in a way that promotes antigen binding. See the Background section and references cited therein. The chemical structure of many FRs is known in detail and these have been reported in a well-known public database See eg., pgs. 25-26, bridging paragraph, (discussing the Kabat database that includes a listing of many FRs.)

Applicants' disclosure provides the precise chemical structure of all eight FRs of the murine cH36 anti-TF antibody. For instance, Figure 12A-D shows the three light chain FR sequences. Also, Figure 13A-D show the corresponding three FR sequences on the heavy chain in precise detail. As can be seen from Figures 12A-D and 13A-D, for instance, each FR in the murine antibody is rather small compared with the larger light or heavy chain in which it resides. Thus,

should the worker wish to manipulate one or more FRs to produce others that are at least about 95% identical to the disclosed FRs, only routine experimentation would be required as the specification makes clear.

As the specification also makes clear, the claimed invention is not limited to any particular humanized version of the murine cH36 antibody. Applicant is of the belief that many humanized FRs that are almost identical (*i.e.*, at least 95% identical) to the preferred FRs shown in Figures 12A-D and Figures 13A-D will bind TF antigen. In support, Applicants have generally pointed to other suitable FRs that can be tested for good TF binding. See pg. 29, line 18 to pg. 31, line 16; pg. 12, lines 18 to pg. 13, line 5. As an example, the specification identifies FRs with particular amino acid substitutions that can be tested. See Figures 12A-D and 13A-D. See also Example 9 (teaching, for instance, how to humanize the murine cH36 antibody and make preferred FRs). Nucleic acids that encode such FRs are also provided, for instance, at pg. 13, line 7 to pg. 15, line 3; and pgs. 43-44, bridging paragraph.

More specifically, the panel of FR sequences provided by Figures 12A-D and 13A-D show several FR sequences that are at least 95% identical to another including FRs for the murine antibody and the preferred HC-08 (fully humanized) antibody. The sequences represent "partially humanized" FRs and can certainly be tested with a minimum of experimentation for good TF binding.

Methods to make and test various FRs according to the invention have been disclosed throughout the application. For instance, see pg. 35 to pg. 37, line 6 (generally describing Applicants' "best fit" approach). Example 9 provides more specific methods for making such FRs as well as other antibody humanization steps.

Accordingly, it is believed that any testing needed to identify or confirm suitable humanized FRs for use with the claimed invention is well within the level of

experimentation permitted by the Federal Circuit. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

A worker in this particular field would be able to use the guidance provided by the instant disclosure to select appropriate FRs that are at least about 95% identical to the specific light chain FRs specified in claim 10, for instance. Any inoperable embodiments of the type described by the rejection could be readily avoided. As described by the Court of Customs and Appeals:

> [M]any patented claims read on vast numbers of inoperative embodiments in the trivial sense that they can and do omit 'factors which must be presumed to be within the level of ordinary skill in the art.' ... There is nothing wrong with this so long as it would be obvious to one of skill in the art how to include these factors in such manner as to make the embodiment operative rather than inoperative. *In re Cook and Merigold*, 169 USPQ 299, 302 (C.C.P.A. 1971) (quoting *In re Skrivan*, 166 USPQ 85, 88 (C.C.P.A. 1970)).

Thus, one of skill having read Applicants' disclosure would know to identify suitable FRs. Even if one assumes, *arguendo*, that one FR did not exhibit acceptable TF binding activity in the context of a particular humanized antibody, that result, by itself, would not support the present enablement rejection. The worker would understand that another FR construct as provided by the specification, could be tested and identified for suitable antigen binding activity.

In view thereof, reconsideration and withdrawal of the enablement rejections are requested.

35 USC §112, first paragraph (written description)

Claims 1-50, 55-58, and 62 stand rejected under 35 USC §112, first paragraph, (written description). Applicants respectfully disagree. The specification as filed originally fully satisfies the written description requirement.

As an initial matter, it is noted that the rejection seems premised on the position that only claims drawn to exemplified invention embodiments satisfy the requirements of Section 112, first paragraph, notwithstanding the broader invention Applicants disclose.

Respectfully, such a position conflicts with established patent law. It is well-recognized that a patentee's invention is properly broader than specific embodiments identified in an application. Thus in *In re Anderson*, the CCPA reversed a rejection under Section 112, first paragraph and noted in particular (176 USPQ at 333):

> What the Patent Office is here apparently attempting is to limit all claims to the specific examples, notwithstanding the clear disclosure of a broader invention. **This it may not do**.... There is no doubt that a patentee's invention may be broader than the particular embodiment shown in his specification. A patentee is not only entitled to narrow claims directed to the preferred embodiment, but also to broad claims which define the invention without a reference to specific instrumentalities. (emphasis added).

Here, the claimed invention is broader than the humanized antibody having the particular LC, HC, and isotype structures mentioned at pg. 6 of the Office Action. As taught throughout Applicant's disclosure, the invention is compatible with a variety of suitable humanized antibodies that bind specifically to human tissue factor.

That said, Applicants believe the specification fully satisfies the written description requirement in view of the subject claims.

As pointed out by the Office, the following document provides guidance on how to satisfy the written description requirement of §112. According to the Guidelines for Examination of Patent Applications Under 35 USC §112, 1¶, "Written Description Requirement (hereinafter "Guidelines"):

> The fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, **as of the filing date sought**, applicant was in **possession** of the now claimed invention (citing *Vas-Cath, Inc.* 935 F.2d at 1563-64, 19USPQ2d at 1117).

See the Federal Register, Vol. 66, pp. 1099-1111, part IB at pg. 1105.

Thus, the correct inquiry is to confirm that Applicant was in possession of the humanized antibody of claim 1, for instance, as of his filing date. As noted by the Office, the Guidelines are flexible and provide several ways in which possession of the claimed invention can be demonstrated as of the application filing date:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in **possession of the claimed invention**, *i.e.*, **complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between structure and function, or some combination of such characteristics**. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.
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> Federal Register, *ibid*, part IIA at pg. 1106.

Indeed, the Federal Circuit held that the written description requirement "may be satisfied by using such descriptive means as words, structures, figures, diagrams, formulas, *etc.*, that fully set forth the claimed invention". See *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

In full compliance with the Guidelines, Applicants respectfully submit that they were in possession of the claimed invention as of their filing date. For instance, Applicants believe that at least the following requirements from the Guidelines have been fully satisfied:

A. Complete or Partial Structure

The specification provides structures for illustrative humanized antibodies that bind TF at pg. 26, line 25 to pg. 27, line 3; pg. 27, line 12 to pg. 28, line 3; pg. 28, line 25 to pg. 34, line 11. Complete structures relating to preferred FR and CDR structures are

provided by Example 9 and Figures 12A-D and 13A-C, for instance. Molecular weights of preferred antibodies are also provided at pg. 18, lines 7-16.

B. Other Physical and/or Chemical Properties

The claimed antibodies bind human tissue factor (TF) specifically. See *e.g.*, the Summary of the Invention.

C. Functional Characteristics Coupled With A Known or Disclosed Correlation Between Structure and Function

As mentioned, the function of the claimed humanized antibody is to bind TF. Figures 12A-D (light chain) and Figures 13A-D (heavy chain), for instance, disclose specific amino acid changes that can be made in the murine antibody FRs on each chain. Further changes in certain CDRs (where permitted) are also exemplified at Fig. 13C. Taken with the rest of Applicants' disclosure, Applicants have provided a detailed "roadmap" that correlates, for example, particular amino acids changes in the FRs (and a certain CDR) to the structure of humanized antibodies that bind TF antigen including the fully humanized HC-08 antibody. See the Examples and Figures 12A-D and 13A-D.

In view thereof, reconsideration and withdrawal of the written description rejection are requested.

35 USC §102(a)

Claims 1-9, 14-20, 43-44, 55-57 and 62 stand rejected as being anticipated by WO 96/40921. While Applicants respectfully disagree with the position taken, basis for it has been addressed by this submission.

In particular, claims 1 and 17 have been amended with language from claims 10 and 12 (both now canceled). Those claims were not considered anticipated by the Office. All remaining claims cited by the Office are dependent from either amended claim 1 or 17. Accordingly, the rejection is moot in view of amended claims 1 and 17.

Reconsideration and withdrawal of the rejection are requested.

35 USC §103(a)

Claims 1-6, 8-9, 55-58 and 62 stand rejected as being obvious over U.S. Pat. No. 5, 223, 427 and the Owens *et al.* (1994) reference. While Applicants disagree with the position taken, basis for the rejection has been addressed by this response.

In particular, claim 1 has been amended with language from claims 10 and 12 (both now canceled). Those claims were not deemed obvious by the Office. All remaining claims cited by the Office are dependent from amended claim 1. Accordingly, there is no basis for maintaining the rejection.

Reconsideration and withdrawal of the rejection are requested.

Double Patenting Rejection

On pages 10-11 of the Action, the Office took the position that certain claims should be rejected under the judicially created doctrine of obviousness-type double patenting in view of U.S. Pat. No. 6,555,319. While Applicants respectfully disagree with the position taken, basis for it has been addressed by this response.

Specifically, claim 1 has been amended with language from claims 10 and 12 (both now canceled). Canceled claims 10 and 12 were not subject to the

double patenting rejection. Thus, there would be no basis for making the rejection on indication of allowable subject matter.

It is believed the application is in condition for allowance, which action is earnestly solicited. Although it is not believed that any further fee is needed to consider this submission, the Office is authorized to charge such fee to our Deposit Account No. **04-1105** if deemed necessary.

Respectfully submitted,

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